TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED / ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	US APPLICATION NO (If known, see 37 CFR 1.5)
P66645US0	09/857465

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/GB99/04031	6 December 1999	5 December 1998

TITLE OF INVENTION

PROCESS FOR PREPARING CHIRAL COMPOUNDS

APPLICANT(S) FOR DO/EO/US

David O'HAGAN

Applicant herein submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information.

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for Internatl. Preliminary Examination was made by the 19th month from earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US)
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the Internatl. Preliminary Examination report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☒ An assignment document for recording. A separate cover sheet compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items or information:

    International Search Report -EPO
    PCT Request Form
    First Page of Publication
    Demand
    International Preliminary Examination Report - with annexes
    Small Entity Declaration (2 sheets)

US APPLICATION NO.(If known, see 37 CFR 1 5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
09/857465	PCT/GB99/04031	P66645US0

	CALCULATIONS	PTO USE ONLY
17. ☒ The following fees are submitted:		
Basic National Fee (37 CFR 1.492(a)(1)-(5)):		
Internatl. prelim. examination fee paid to USPTO (37 CFR 1.492 (a) (1)) . . $690.00		
No international preliminary examination fee paid to USPTO (37 CFR 1.492 (a) (2)) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) . . $710.00		
Neither international preliminary examination fee (37 CFR 1.492 (a) (3)) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO) **$1000.00**		
International preliminary examination fee paid to USPTO (37 CFR 1.492 (a) (4)) and all claims satisfied provisions of PCT Article 33(2)-(4) $100.00		
Search Report prepared by the EPO or JPO (37 CFR 1.492 (a) (5)) **$860.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 860.00	
Surcharge of $130.00 for furnishing the **oath or declaration** later than ☐ **20** ☐ **30** months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

Claims	**Number Filed**	**Number Extra**	Rate		
Total Claims	**14** - 20 =	-0-	x $18.00	$	
Independent Claims	**1** - 3 =	-0-	x $80.00	$	
Multiple Dependent Claim(s) (if applicable)			+ $270.00	$	
TOTAL OF ABOVE CALCULATIONS =				$ 860.00	
Reduction by 1/2 for filing by **small entity**.				$ 430.00	
SUBTOTAL =				$ 430.00	
Processing fee of $130 for furnishing the **English translation** later than ☐ **20** ☐ **30** months from the earliest claimed priority date (37 CFR 1.492(f))				$	
TOTAL NATIONAL FEE =				$ 430.00	
Fee of $40.00 for recording the enclosed **assignment** (37 CFR 1.21(h)). Assignment must be accompanied by appropriate cover sheet (37 CFR 3.28, 3.31).				$ 40.00	
TOTAL FEES ENCLOSED =				$ 470.00	
				Amt. to be refunded:	$
				Amt. charged:	$

a. ☒ A check in the amount of $ 470.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. **06-1358** in the amount of $ ____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge my account any additional fees set forth in §1.492 during the pendency of this application, or credit any overpayment to Deposit Account No. **06-1358**. A duplicate copy of this sheet is enclosed.

SEND ALL CORRESPONDENCE TO:

JACOBSON HOLMAN PLLC
400 7th Street, N.W., Suite 600
Washington, DC 20004
202-638-6666
CUSTOMER NUMBER: 00136

By Harvey B Jacobson Jr.
Harvey B. Jacobson, Jr.
Reg. No. 20,851

JPH&S 3/95

Law Offices of
JACOBSON HOLMAN
PROFESSIONAL LIMITED LIABILITY COMPANY
THE JENIFER BUILDING
400 SEVENTH STREET, N.W.
WASHINGTON, DC 20004

Attny's Docket No. P66645US0

SMALL ENTITY DECLARATION
[37 CFR 1.9(c-f)]

Each undersigned declares that:

(1) ☒ the application attached hereto.

(2) ☐ U.S. Application Serial No. _____, filed _____

(3) ☐ U.S. Patent No. _____ Issued _____

is entitled to the benefits of "small entity" status for paying reduced fees under 35 USC 41(a) and (b) to the Patent and Trademark Office by virtue of the following:

(4) ☐ Each undersigned declares that he/she qualifies as an independent inventor, or would qualify had he/she made the as defined in 37 CFR 1.9(c).

(5) ☒ The undersigned declares that he/she is an official empowered to act on behalf of the concern identified below; that concern qualifies as a small business concern as defined in 37 CFR 1.9(d); that exclusive rights to the invention have been conveyed to and remain with the small business concern, or if the rights are not exclusive, that all other rights belong to small entities as defined in 37 CFR 1.9.

(6) ☐ The undersigned declares that he/she is an official empowered to act on behalf of the organization identified below; that organization qualifies as a nonprofit organization as defined in

(a) ☐ 37 CFR 1.9(e)(1)

(b) ☐ 37 CFR 1.9(e)(2)

(c) ☐ 37 CFR 1.9(e)(3)

(d) ☐ 37 CFR 1.9(e)(4) State law of _____;

that exclusive rights to the invention have been conveyed to and remain with the organization, or if the rights are not exclusive, that all other rights belong to organizations as defined in 37 CFR 1.9.

(7) Each person, concern or organization to which I/we have assigned, granted, conveyed or licensed, or am under an under contract or law to assign, grant, convey, or license any rights in the invention is listed below:

(a) ☒ no such person, concern or organization

(b) ☐ persons, concerns or organization listed below

[a separate declaration is required from *each* named person, concern or organization having rights to this invention averring to their status as "small entities."]

Full Name _____

Address _____

☐ Individual ☐ Small Business Concern ☒ Nonprofit Organization

I/we acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement of small entity prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

I/we hereby declare all statements made herein of his/her own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application, any patent issued thereon, or any patent to which this declaration is directed.

(8)

Typed Name of Inventor	Signature	Date
Typed Name of Inventor	Signature	Date
Typed Name of Inventor	Signature	Date
Typed Name of Inventor	Signature	Date

(9) University of Durham
Name of Small Business Concern or Nonprofit Organization

PAULINA LUSAKA By _____ 23/5/01
Typed Name Signature Date

TREASURER
Title of Signatory

Law Offices of
JACOBSON HOLMAN
PROFESSIONAL LIMITED LIABILITY COMPANY
THE JENIFER BUILDING
400 SEVENTH STREET, N.W.
WASHINGTON, DC 20004

Attny's Docket No. P66645US0

SMALL ENTITY DECLARATION
[37 CFR 1.9(c-f)]

Each undersigned declares that:

(1) [X] the application attached hereto.

(2) [ ] U.S. Application Serial No. _____ filed _____.

(3) [ ] U.S. Patent No. _____ issued _____.

is entitled to the benefits of "small entity" status for paying reduced fees under 35 USC 41(a) and (b) in the Patent and Trademark Office by virtue of the following:

(4) [X] Each undersigned declares that he/she qualifies as an independent inventor, or would qualify had he/she made the as defined in 37 CFR 1.9(c).

(5) [ ] The undersigned declares that he/she is an official empowered to act on behalf of the concern identified below; that concern qualifies as a small business concern as defined in 37 CFR 1.9(d); that exclusive rights to the invention have been conveyed to and remain with the small business concern, or if the rights are not exclusive, that all other rights belong to small entities as defined in 37 CFR 1.9.

(6) [ ] The undersigned declares that he/she is an official empowered to act on behalf of the organization identified below; that organization qualifies as a nonprofit organization as defined in

(a) [ ] 37 CFR 1.9(e)(1)

(b) [ ] 37 CFR 1.9(e)(2)

(c) [ ] 37 CFR 1.9(e)(3)

(d) [ ] 37 CFR 1.9(e)(4) State law of _____;

that exclusive rights to the invention have been conveyed to and remain with the organization, or if the rights are not exclusive, that all other rights belong to organizations as defined in 37 CFR 1.9.

(7) Each person, concern or organization to which I/we have assigned, granted, conveyed or licensed, or am under an under contract or law to assign, grant, convey, or license any rights in the invention is listed below:

(a) [ ] no such person, concern or organization

(b) [X] persons, concerns or organization listed below

[a separate declaration is required from *each* named person, concern or organization having rights to this invention averring to their status as "small entities."]

Full Name University of Durham

Address South Road, Durham DH1 3LE, United Kingdom

[ ] Individual [ ] Small Business Concern [X] Nonprofit Organization

I/we acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement of small entity prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

I/we hereby declare all statements made herein of his/her own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application, any patent issued thereon, or any patent to which this declaration is directed.

(8) David O'HAGAN — Typed Name of Inventor | Signature | 25.05.01 Date

Typed Name of Inventor | Signature | Date

Typed Name of Inventor | Signature | Date

Typed Name of Inventor | Signature | Date

(9) _____
Name of Small Business Concern or Nonprofit Organization

By

Typed Name | Signature | Date

Title of Signatory

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: David O'HAGAN

Serial No.: New

Filing Date: June 5, 2001

For: PROCESS FOR PREPARING CHIRAL COMPOUNDS

PRELIMINARY AMENDMENT

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

Prior to initial examination, please amend the above-identified application as follows:

IN THE CLAIMS

Please amend claims 3 through 14 as follows:

3. (amended) Process as claimed in Claim 1 wherein R^3 is selected from ethenyl, ethynyl and optionally substituted phenyl.

4. (amended) Process as claimed in Claim 1 wherein at least one and preferably both of R^3 are aryl.

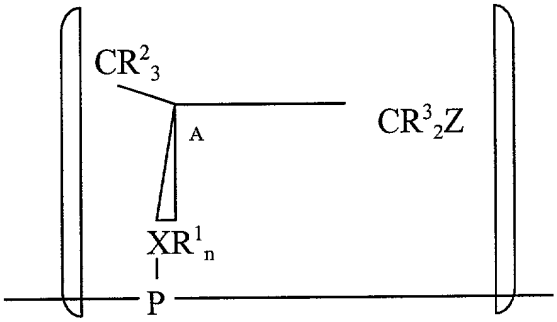
5. (amended) Process as claimed in Claim 1 wherein R^2 is selected from optionally hydroxy, halo or alkoxy substituted branched and straight chain C_1-$_6$ alkyl, including methyl, ethyl, i-propyl, i-butyl, t-butyl; and aryl including phenyl and benzyl.

6. (amended) Process as claimed in Claim 1 wherein X is nitrogen wherein n is 1 and R^1 is H, i.e. the compound is a primary amine.

7. (amended) Process as claimed in Claim 1 wherein a catalyst comprises Pd with C as catalytic support.

8. (amended) Process as claimed in Claim 1 wherein a fluorination agent is liquid phase HF-pyridine.

9. (amended) *Process for preparation of* enantiomerically pure polymer comprising a repeating unit of the formula Ii:

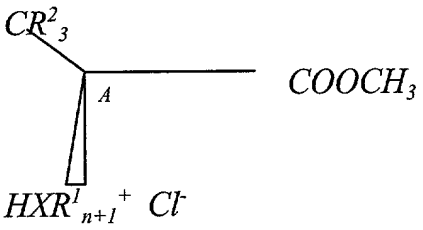
(Ii) 

wherein P is derived from a polymerisable monomer or oligomer and X, R^1, R^2, R^3, Z and A are as hereinbefore defined in Claim 1; and

wherein a polymerisable monomer is selected from the group consisting of: an epoxy resin; an addition-polymerisation resin; a formaldehyde condensate resin; a cyanate resin; and an isocyanate resin; polyaromatics; monomers of natural polymers including carbohydrates, polypeptides and proteins including starch, celluloses, collagen, gelatin, dextrans, alginates, chitin and chitosan; and monomers of biodegradeable and/or biocompatible polymers including poly(lactic acid), poly(glycolic acid), polycaprolactone, polyorthoesters, polyanhydrides, polyaminoacids and azo polymers; and mixtures thereof.

10. (amended) *Process for preparation of* a library of *enantiomerically pure* compounds comprising:

reacting one or more compounds of formula IV

(IV) 

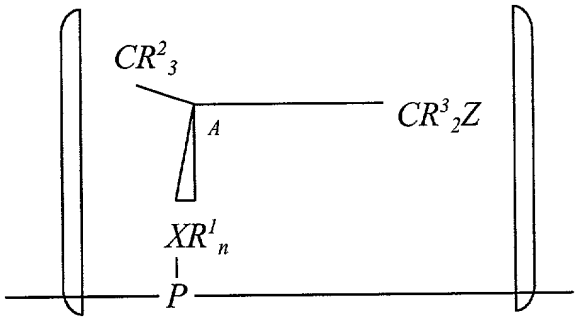
Wherein R^1, R^2 *and A are as hereinbefore defined in Claim 1*

with a plurality of compounds of formula V R^2MgBr, and converting via compounds of formula II as hereinbefore defined *in Claim 1* to compounds of formula I as hereinbefore defined *in Claim 1*; and

optionally labelling the support or vessel with means to identify the synthetic history of the supported or contained compound.

11. (amended) *Enantiomerically pure* compound of the formula I as hereinbefore defined in Claim 1 wherein A, Z and R^1 to R^3 are as hereinbefore defined, X is N and n is 1.

12. (amended) *Enantiomerically pure polymer comprising a repeating unit of the formula Ii:*

(Ii) 

wherein *P is derived from a polymerisable monomer or oligomer selected from the group consisting of: an epoxy resin; an addition-polymerisation resin; a formaldehyde condensate resin; a cyanate resin; and an isocyanate resin; polyaromatics; monomers of natural polymers including carbohydrates, polypeptides and proteins including starch, celluloses, collagen, gelatin, dextrans, alginates, chitin and chitosan; and monomers of biodegradeable and/or biocompatible polymers including poly(lactic acid), poly(glycolic acid), polycaprolactone, polyorthoesters; and*

X, R^1, R^2, R^3, Z and A are as hereinbefore defined In Claim 1.

13. (amended) Library of enantiomerically pure compounds of formula I as hereinbefore defined *in Claim 11.*

14. (amended) Pharmaceutical, veterinary product or agrochemical composition comprising an enantiomerically pure compound of formula I, Ii or Iii as hereinbefore defined *in Claim 11* with suitable diluents, adjuvants, carriers.

REMARKS

The foregoing Preliminary Amendment is requested in order to delete the multiple dependent claims and avoid paying the multiple dependent claims fee.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE.**"

Early action on the merits is respectfully requested.

Respectfully submitted,

JACOBSON HOLMAN PLLC

By _____
Harvey B. Jacobson, Jr.
Reg. No. 20,851

400 Seventh Street, N.W.
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(202) 638-6666

Atty. Docket: P66645US0
Date: June 5, 2001
HBJ/cmf

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS

3. (amended) Process as claimed in Claim 1 [any one of Claims 1 and 2] wherein R^3 is selected from ethenyl, ethynyl and optionally substituted phenyl.

4. (amended) Process as claimed in Claim 1 [any one of Claims 1-3] wherein at least one and preferably both of R^3 are aryl.

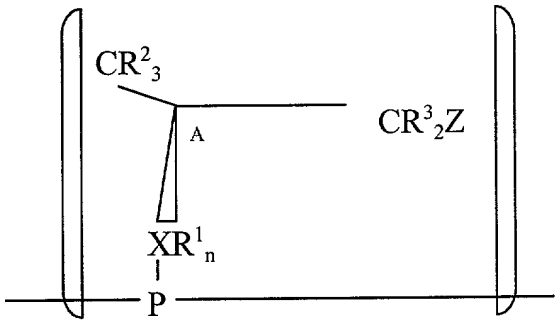
5. (amended) Process as claimed in Claim 1 [any one of Claims 1-4] wherein R^2 is selected from optionally hydroxy, halo or alkoxy substituted branched and straight chain C_1-$_6$ alkyl, including methyl, ethyl, i-propyl, i-butyl, t-butyl; and aryl including phenyl and benzyl.

6. (amended) Process as claimed in Claim 1 [any one Claims 1 to 5] wherein X is nitrogen wherein n is 1 and R^1 is H, i.e. the compound is a primary amine.

7. (amended) Process as claimed in Claim 1 [any one of Claims 1-6] wherein a catalyst comprises Pd with C as catalytic support.

8. (amended) Process as claimed in Claim 1 [any of Claims 1-7] wherein a fluorination agent is liquid phase HF-pyridine.

9. (amended) [[13,14[16,17]].] *Process for preparation of [a compound of the formula I as hereinbefore defined in any of Claims 1 to 8 which is a process for the* preparation of] enantiomerically pure [enantiomerically pure] polymer comprising a repeating unit of the formula Ii:

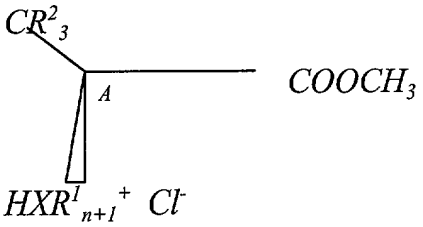
(Ii) 

wherein P is derived from a polymerisable monomer or oligomer and X, R^1, R^2, R^3, Z and A are as hereinbefore defined in [any of] Claim[s] 1 [to 6]; and

wherein a polymerisable monomer is selected from the group consisting of: an epoxy resin; an addition-polymerisation resin; a formaldehyde condensate resin; a cyanate resin; and an isocyanate resin; polyaromatics; monomers of natural polymers including carbohydrates, polypeptides and proteins including starch, celluloses, collagen, gelatin, dextrans, alginates, chitin and chitosan; and monomers of biodegradeable and/or biocompatible polymers including poly(lactic acid), poly(glycolic acid), polycaprolactone, polyorthoesters, polyanhydrides, polyaminoacids and azo polymers; and mixtures thereof.

10. (amended) [[17,18[20,21]].] *Process for preparation of [enantiomerically pure compounds of formula I as hereinbefore defined In any of Claims 1 to 8 which is a process for the* preparation of] a library of <u>*enantiomerically pure*</u> compounds comprising:

reacting one or more compounds of formula IV:

(IV) 

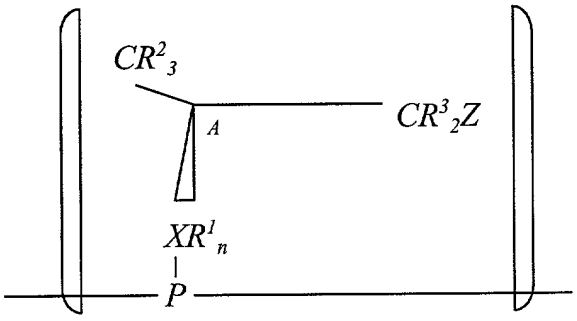
Wherein *R^1, R^2 and A are as hereinbefore defined in [any of] Claim[s] 1[to 6]*

with a plurality of compounds of formula V R^2MgBr, and converting via compounds of formula II as hereinbefore defined *in Claim 1 [to 6]* to compounds of formula I as hereinbefore defined *in [any of] Claim[s] 1[to 6]*; and

optionally labelling the support or vessel with means to identify the synthetic history of the supported or contained compound.

11. (amended) [[12].] *Enantiomerically pure* compound of the formula I as hereinbefore defined in Claim 1 [any of Claims 1 to 6] wherein A, Z and R^1 to R^3 are as hereinbefore defined, X is N and n is 1.

12. (amended) [[15[18]].] *Enantiomerically pure polymer comprising a repeating unit of the formula Ii:*

(Ii) 

wherein *P is derived from a polymerisable monomer or oligomer selected from the group consisting of: an epoxy resin; an addition-polymerisation resin; a formaldehyde condensate resin; a cyanate resin; and an isocyanate resin;*

polyaromatics; monomers of natural polymers including carbohydrates, polypeptides and proteins including starch, celluloses, collagen, gelatin, dextrans, alginates, chitin and chitosan; and monomers of biodegradeable and/or biocompatible polymers including poly(lactic acid), poly(glycolic acid), polycaprolactone, polyorthoesters; and

X, R^1, R^2, R^3, Z and A are as hereinbefore defined In Claim 1 [any of Claims 1 to 6].

13. (amended) [[19 [22]].] Library of enantiomerically pure compounds of formula I as hereinbefore defined *in Claim 11.*

14. (amended) [[20 [23]].] Pharmaceutical, veterinary product or agrochemical composition comprising an enantiomerically pure compound of formula I, Ii or Iii as hereinbefore defined *in Claim 11 [any of Claims 11 – 13]* with suitable diluents, adjuvants, carriers.

PROCESS FOR PREPARING CHIRAL COMPOUNDS

The present invention relates to a process for the preparation of a class of enantiomerically pure chiral compounds, the compounds obtained thereby and novel compounds, compositions thereof and the use thereof as or in the preparation of a pharmaceutical, veterinary product, agrochemical, polymer, library of compounds and their respective intermediates.

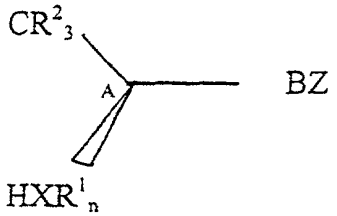
Efficient and simple synthesis of known and novel compounds can be the key to commercial success and may also lead to further development and discoveries enabled by availability of compounds in significant purities, yields and the like. Nevertheless development of new synthetic routes is costly and time consuming, without the guarantee of success.

Tet: Asymm, 1997, 8(1), 149-153 discloses the synthesis of the corresponding excluded pyrrolidine which is a known chiral compound, but makes no reference to synthesis of analogues of any class of analogues, thus implies a unique synthesis for the compound alone.

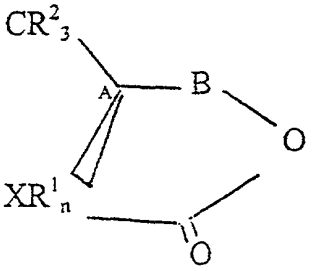
The authors have now found, according to the present invention, that the synthesis is effective for a distinct class of compounds having potential as or in the preparation of organic fine chemicals and polymers.

We have now surprisingly found a process for synthesising a class of compounds in novel manner to produce enantiomerically pure hetero compounds.

Accordingly in a first aspect there is provided a process for the preparation of chiral compounds of formula I:

(I) 

comprising contacting a compound of formula II:

(II) 

with a source of hydrogen or halide;

wherein A is a chiral centre;

X is selected from oxygen, sulphur and nitrogen;

n is selected from 0 and 1 and is equal to the valence of X less 2;

Each R^1 is independently selected from hydrogen, straight chain and branched, saturated and unsaturated C_{1-8} hydrocarbon optionally substituted by one or more hydroxy, halo, aryl, cyclo C_{1-8} alkyl and the like;

B is a fragment CR^3_2 wherein each R^3 is independently selected from hydrogen, halo, azides and cyanides; straight and branched chain, saturated and unsaturated C_{1-4} alkyl, alkenyl and alkynyl and aryl, each optionally substituted by hydroxy, halo, saturated or unsaturated C_{1-4} alkyl, alkenyl or

alkynyl, aryl, cyclo C_{1-6} alkyl, carbonyl, carboxyl, amino, amido, (thio)ether, haloalkyl, silylalkyl and the like;

Z is hydrogen or halogen;

each R^2 is independently selected from hydrogen, straight chain and branched, saturated and unsaturated C_{1-8} alkyl, optionally substituted by hydroxy, halo, aryl, cyclo C_{1-6} alkyl, carbonyl, carboxyl, amino, amido, (thio)ether and the like; and

one of R^1 and one of R^2 together may form an alkylene group as part of a heterocyclic ring;

with the proviso that when X is nitrogen, n is 1, one of R^1 and two of R^2 are hydrogen, BZ is $CHPh_2$, the other R^1 and R^2 do not form together a five membered heterocyclic (pyrrolidone) ring.

Preferably X is nitrogen whereby n is 1.

Preferably B is a fragment CR^3_2 wherein R^3 is selected from ethenyl, propenyl ethynyl and propynyl, optionally substituted phenyl, for example 4-methoxy or 4-perfluoryl alkyl phenyl, naphthyl, methyl phenyl and the like.

More preferably B is a group as hereinbefore defined wherein at least one and preferably both of R^3 are aryl, more preferably optionally substituted phenyl.

Preferably Z is selected from hydrogen, chloro and fluoro, more preferably hydrogen and fluoro.

Preferably R^2 is selected from optionally hydroxy, halo, alkoxy substituted branched and straight chain C_{1-6} alkyl, including methyl, ethyl, i-propyl, i-butyl, t-butyl; and aryl including phenyl and benzyl.

Preferably X is nitrogen wherein n is 1 and R^1 does not form a cyclic ring with one of R^2, i.e. the compound is a non cyclic secondary amine, or R^1 is H, and R^2 is other than H, i.e. the compound is a primary amine.

Without being limited to this theory it is thought that the conversion according to the process of the invention proceeds via a substitution with subsequent decarboxylation or decarboxylation with subsequent quenching.

Contacting the compound of formula II as hereinbefore defined may be in the presence of a catalyst which may be homogeneous or heterogeneous, and is preferably heterogeneous, or of an agent which may be gaseous or liquid and is preferably liquid.

The catalyst may be selected from any catalyst suitable for the conversion as hereinbefore defined. Preferably the catalyst comprises a hydrogenation or fluorination catalyst or agent. A hydrogenation catalyst suitably comprises a metal adapted to catalyse a hydrogenation reaction, for example selected from the transition metals of Group VIII of the Periodic Table of the Elements, preferably selected from Pt, Pd, Ni, Co, Cu, Ru, Fe and Ag and mixtures thereof. The catalyst may be in the form of the metal(s) or salts thereof, optionally in the presence of or including additional catalytic components or catalytic supports such as C. More preferably the catalyst

comprises palladium and carbon, and reaction is in the presence of gaseous hydrogen.

A fluorination agent suitably comprises a source of fluorine associated with an activating component adapted to facilitate fluorination reaction, for example liquid phase HF and a carrier, preferably HF-pyridine (Olah's reagent).

The catalyst or agent is present in catalytically or transformationally effective amount.

The process may be carried out with use of any additional solvents, and may be carried out at reduced, ambient or elevated temperature and/or pressure or a combination thereof in sequence. Gaseous reaction is preferably carried out at ambient temperature and elevated pressure in the range 1-10 atm and liquid phase reaction at ambient pressure and temperature in the range 0 – 20 °C.

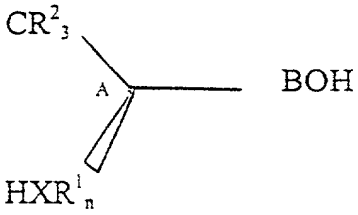
The process of the invention is preferably suitable for the preparation of pharmaceutical, veterinary product, agrochemical and polymeric compounds and libraries of such compounds, and their synthetic intermediates. It is a particular advantage of the process of the invention that such compounds may be readily prepared in which B is analogous electronically and/or sterically to characteristic groupings in known pharmaceutical, veterinary product and agrochemicals. The process therefore provides a known route to access compounds and whole ranges of new analogues, wherein the group B is as hereinbefore defined.

Alternatively the process as hereinbefore defined is suited for the preparation of metal complexes as asymmetric catalysts.

In a further aspect of the invention there is provided a class of novel enantiomerically pure chiral hetero compounds of the formula I as hereinbefore defined wherein A, B, Z and R^1 are as hereinbefore defined, X is N and n is 1 with the exception that R^2 is not phenyl or benzyl when R^1 is hydrogen, BH is phenyl or CH_3 and Z is H.

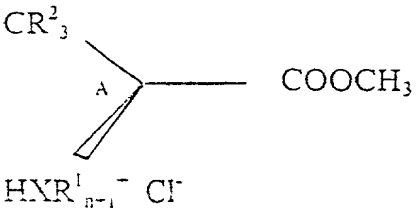
Compounds of the formula II as hereinbefore defined may be obtained commercially or prepared by known means. Akiba *et al*, Tetrahedron, 1994, 50 (13), 3905 discloses the preparation of a compound of formula II by cyclisation of amino alcohol with trichloromethyl chloroformate ($Cl_3COCOCl$) in the presence of triethylamine (Et_3N). Using this process compounds of formula II are obtained from compounds of formula III:

(III)



Intermediate compounds of formula III as hereinbefore defined may be obtained commercially or using the process, for example of Gawley and Zhang, J. Org. Chem., 1996, 61, 8103, and Itsuno *et al*, J. Chem. Soc., Perkin Trans. I, 1985, 2039. In these publications is taught the preparation of a compound of formula III as hereinbefore defined by reaction of a compound of formula IV:

(IV)



with a compound of formula V:

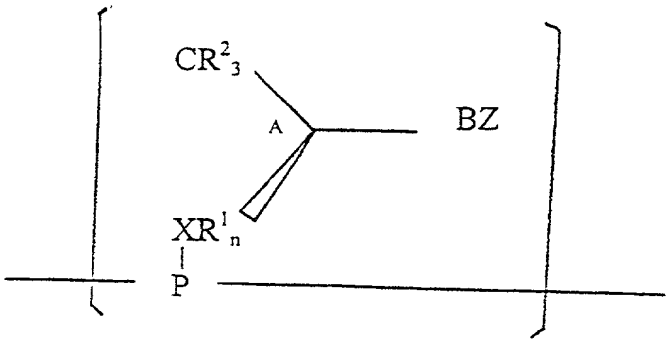
(V) R^2MgBr.

Reaction is preferably under reflux in cold solvent.

Compounds of formula IV and V are commercially available or may be synthesised by known means.

In a further aspect of the invention there is provided a process for the preparation of enantiomerically pure chiral polymers comprising a repeating unit of the formula Ii:

(Ii)



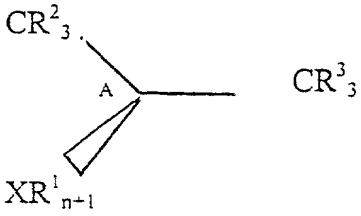
wherein P is derived from a polymerisable monomer or oligomer and X, R^1, R^2, B, Z and A are as hereinbefore defined.

Polymerisable monomers may be any known monomers, for example selected from monomers of thermoset and thermoplast polymers and mixtures thereof, including monomers preferably selected from the group consisting of: an epoxy resin such as an epoxy resin derived from the mono or poly-glycidyl derivative of one or more of the group of compounds consisting of aromatic diamines, aromatic monoprimary amines, aminophenols, polyhydric phenols, polyhydric alcohols, polycarboxylic acids and the like; an addition-polymerisation resin, such as a bis-maleimide resin, acrylic, vinyl or unsaturated polyester; a formaldehyde condensate

resin, such as a formaldehyde-phenol resin, urea, melamine or phenol resin; a cyanate resin; and an isocyanate resin; polyaromatics such as polysulphones and polyethersulphones; monomers of natural polymers including carbohydrates, polypeptides and proteins including starch, celluloses, collagen, gelatin, dextrans, alginates, chitin and chitosan; and monomers of biodegradeable and/or biocompatible polymers such as polyesters including poly(lactic acid), poly(glycolic acid), polycaprolactone and the like, polyorthoesters, polyanhydrides, polyaminoacids and azo

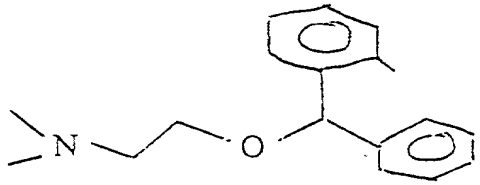
polymers, for example for the delivery of a pharmaceutical, veterinary product or agrochemical *in situ* .

In a further aspect of the invention there is provided a process for the preparation of compounds of the formula Iii:

(Iii) 

by the functional modification of a compound of formula I as hereinbefore defined to include additional groups R^1 and R^3 or the interconversion of one compound of formula I as hereinbefore defined to another compound of formula I as hereinbefore defined.

Preferably the compound of formula Iii as hereinbefore defined is a spatial, electronic or reactive analogue of a known pharmaceutical, veterinary product. or agrochemical, for example of a neuro active compound. such as the compound orphenadrine of formula:



for use in treating Parkinson's Disease or of cardiovascular or gastro-intestinal drugs, immunosuppresants, respiratory agents, musculoskeletal and joint disease drugs, immunological products and vaccines, pest control agents, plant growth control agents, plant disease control agents and the like.

In a further aspect of the invention there is provided the use of one or more compounds of formula I as hereinbefore defined in the preparation of a library of compounds comprising:

reacting one or more compounds of formula I as hereinbefore defined with one or more substrates which are supported or contained in solid or liquid phase each on an individual support or within an individual vessel; and

labelling the support or vessel with means to identify the synthetic history of the supported or contained compound.

The process for preparing a library of compounds may employ any techniques as known in the art of combinatorial chemistry.

In a further aspect of the invention there is provided a process for the preparation of a library of compounds of formula I as hereinbefore defined comprising:

reacting one or more compounds of formula IV as hereinbefore defined with a plurality of compounds of formula V as hereinbefore defined, and converting via compounds of formula II as hereinbefore defined to compounds of formula I as hereinbefore defined; and

optionally labelling the support or vessel with means to identify the synthetic history of the supported or contained compound.

In a further aspect of the invention there is provided a library of compounds of formula I, II or III as hereinbefore defined.

Preferably the library of compounds is suitable for any of the hereinbefore defined uses. The library may be provided in the form of a kit of sample boxes for the intended use. The library may contain two or more compounds, for example ten or more compounds, preferably comprises 50-1,000 compounds of any given formula as hereinbefore defined, optionally including synthetic history identification.

In a further aspect of the invention there is provided a pharmaceutical, veterinary product or agrochemical composition comprising a compound of formula I as hereinbefore defined or derivatives thereof together with suitable diluents, adjuvants, carriers and the like.

The invention is now illustrated in non limiting manner with reference to the examples and Table 1.

Ex	I	Z	R2	R2	R2	R3	R3	IV ester	III alcohol	II oxazolid -inone
1.1	4	H	CH3	CH3	H	Ph	Ph	Methyl 1	butanol 2	3
1.2	8	H	CH2Ph	H	H	Ph	Ph	ethyl 5	Butanol 6	7
1.3	12	H	H	H	H	Ph	Ph	Methyl 9	Butanol 10	11
1.4	15	H	C2H5	CH3	H	Ph	Ph	Methyl	Pentanol 13	14
1.5	18	H	IPr	H	H	Ph	Ph	Methyl	Pentanol 16	17

2.1	19	F	C2H5	CH3	H	Ph	Ph	Methyl	13	14
2.2	20	F	iPr	H	H	Ph	Ph	Methyl	16	17
2.3	21	F	-pyrrolidine-		H	Ph	Ph	Tet:	Tet:	Tet:

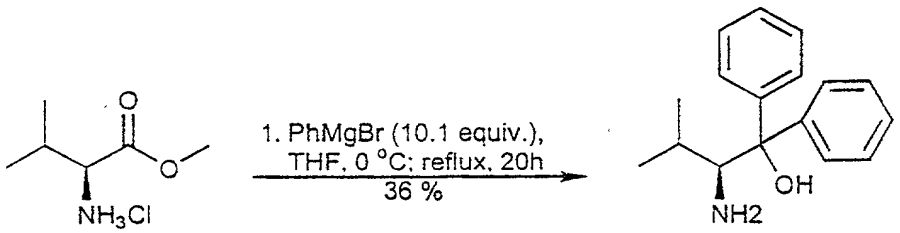
Examples - Synthesis of Novel Chiral Amines

1. Chiral Amines wherein Z is H

1.1 Synthesis of (S)-2-amino-1,1-diphenyl-3-methyl-1-butane (2)

Synthesis of (S)-2-amino-1,1-diphenyl-3-methyl-1-butanol (2)

The title compound (2) was readily prepared by the addition of L-valine methyl ester hydrochloride (1) to phenylmagnesium bromide, as depicted in **Scheme 1**, following the modified method described by Gawley[i] and Zhang (1996), and Itsuno[ii] *et al.* (1985).



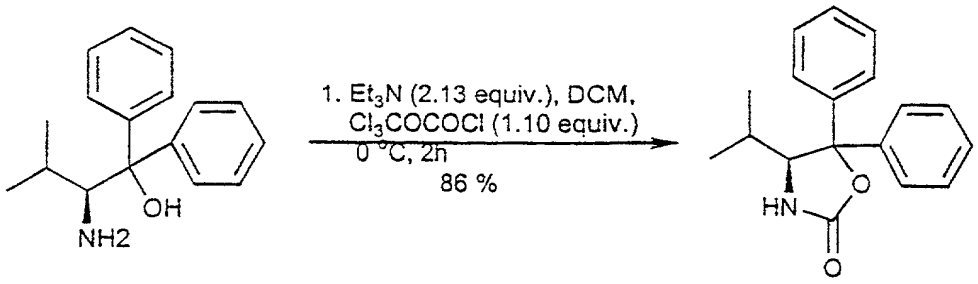
(1) (2)

Scheme 1

Purification over silica gel, gave (2) as a white solid in moderate yield (36 %).

Synthesis of (S)-4-isopropyl-5,5-diphenyl-2-oxazolidinone (3)

In the event, the title compound (3) was readily prepared by the cyclisation of aminoalcohol (2) with trichloromethyl chloroformate ($Cl_3COCOCl$) in the presence of triethylamine (Et_3N), as shown in **Scheme 2**, following the method described by Akiba[iii] *et al.* (1994).



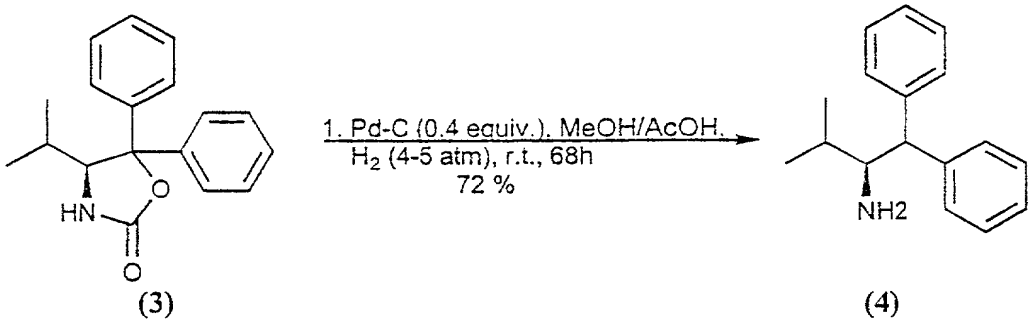
(2) (3)

Scheme 2

Upon work-up, the solid residue was loaded on to a sintered funnel and then washed with diethyl ether to obtain the title compound (3) as a white solid in good yield (86 %).

Synthesis of (S)-2-amino-3-methyl-1,1-diphenylbutane (4)

In the presence of a catalytic amount of palladium on activated carbon, 2-oxazolidinone (3) was finally submitted to the hydrogenation in a mixture of AcOH and MeOH under 4-5 atm. pressure, as illustrated in **Scheme 3**.



(3) (4)

Scheme 3

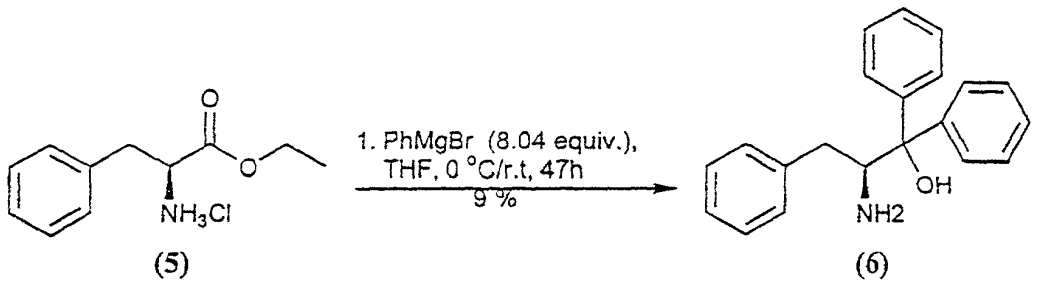
Upon filtration and re-crystallisation from petroleum ether, the title compound (4) was generated as a white solid in good yield (72 %).

1.2 Synthesis of (S)-2-amino-1,1,3-triphenyl-1-propane (6)

Synthesis of (S)-2-amino-1,1,3-triphenyl-1-propanol (6)

The title compound (6), following the modified literature methods of Itsuno[ii,iv] *et al.* (1985), Weber[v] *et al.* (1995) and Dammast and Reißig[vi] (1993),

was readily prepared by the portionwise addition of L-phenylalanine ethyl ester hydrochloride (5) to phenylmagnesium bromide, as depicted in **Scheme 4**.



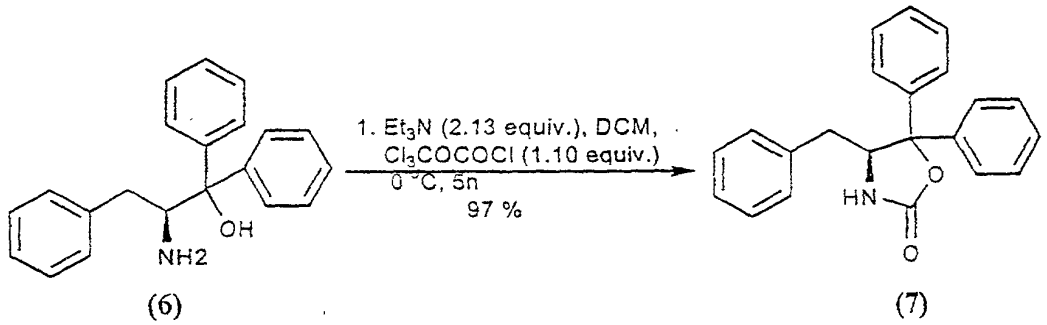
(5) (6)

Scheme 4

Recrystallisation gave the title compound (6) as a white solid in low yield (9 %).

Synthesis of (S)-4-benzyl-5,5-diphenyl -2-oxazolidinone (7)

In the event, the title compound (7) was readily prepared by the cyclisation of aminoalcohol (6) with trichloromethyl chloroformate ($Cl_3COCOCl$) in the presence of triethylamine (Et_3N), as shown in **Scheme 5**, following the method described by Akiba[iii] *et al.* (1994).



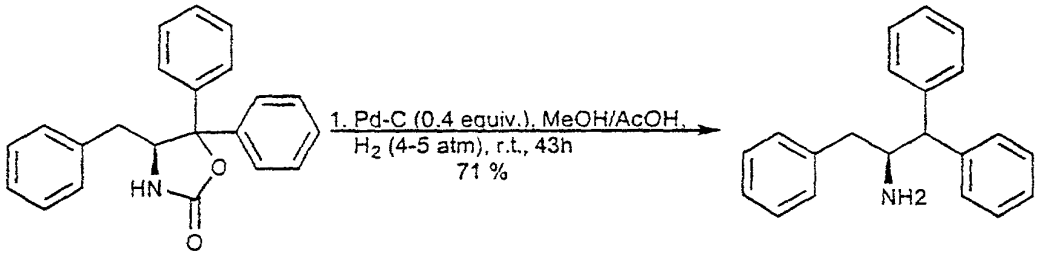
(6) (7)

Scheme 5

Upon work-up, the solid residue was loaded on to a sintered funnel and then washed with diethyl ether to obtain the title compound (7) as a white solid in excellent yield (97 %).

Synthesis of (S)-2-amino-1,1,3-triphenyl-propane (8)

In the presence of a catalytic amount of palladium on activated carbon, 2-oxazolidinone (7) was finally subjected to the hydrogenation in a mixture of AcOH and MeOH under 4-5 atm. pressure, as illustrated in **Scheme 6**.



(7) (8)

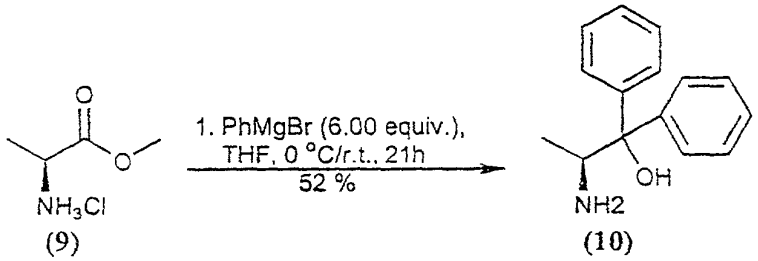
Scheme 6

Upon filtration and purification over silica gel, eluting with a 3:7 and 4:6 mixture of AcOEt and petrol, the title compound (8) was obtained as a light-brown solid in good yield (71 %).

1.3 Synthesis of (S)-2-amino-1,1-diphenyl-1-propanol (10)

Synthesis of (S)-2-amino-1,1-diphenyl-1-propanol (10)

The title compound **(10)**, following the literature methods of Itsuno[ii] *et al.* (1985), Weber[v] *et al.* (1995) and Dammast[vi] and Reißig (1993), was readily prepared by the portionwise addition of L-alanine methy ester hydrochloride **(9)** to phenylmagnesium bromide, as depicted in **Scheme 7**.



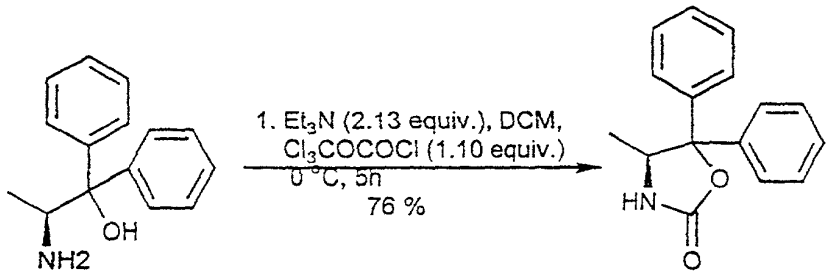
(9) (10)

Scheme 7

Flash column chromatography, eluting with dichloromethane and then further elution with a mixture of AcOEt and petrol, ranging from 15 % up to 100 %, gave the title compound (10) as a white solid in moderate yield (52 %).

Synthesis of (S)-4-methyl-5,5-diphenyl-2-oxazolidinone (11)

In the event, the title compound (11) was readily prepared by the cyclisation of aminoalcohol (10) with trichloromethyl chloroformate ($Cl_3COCOCl$) in the presence of triethylamine (Et_3N), as shown in **Scheme 8**, following the method described by Akiba[iii] *et al.* (1994).



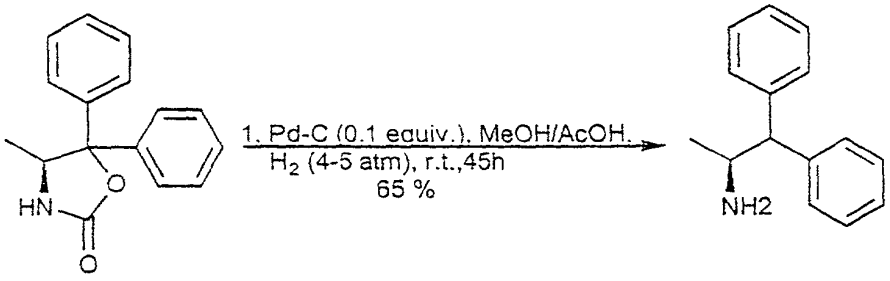
(10) (11)

Scheme 8

Upon work-up, the solid residue was loaded on to a sintered funnel and then washed with diethyl ether to obtain the title compound (11) as a white solid in good yield (76 %).

Synthesis of (S)-2-amino-1,1-diphenyl-propane (12)

In the presence of a catalytic amount of palladium on activated carbon, 2-oxazolidinone (11) was finally subjected to the hydrogenation in a mixture of AcOH and MeOH under 4-5 atm. pressure, as illustrated in **Scheme 9**.



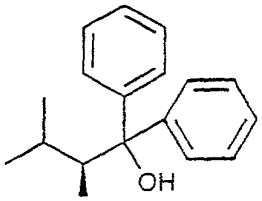
(11) (12)

Scheme 9

Upon filtration and purification by dry- flash column chromatography, eluting first with AcOEt, and then with a mixture of MeOH and AcOEt, ranging from 5 % up to 30 %, gave the title compound (12) as a white solid in moderate yield (71 %).

Experimental

1.1 (S)-2-amino-1,1-diphenyl-3-methyl-1-butanol (2)

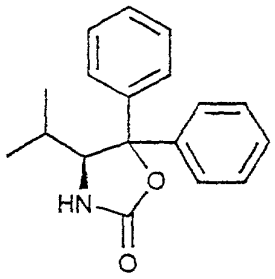


(2)

L-Valine methyl ester hydrochloride (9.9 g, 59.06 mmol) was added portionwise to a 1.0 M solution of phenylmagnesium bromide (108.8 g, 0.6 mol) in THF at 0 °C and heated at reflux for 20h. After quenching with crushed ice and NH_4Cl salt, the organic layer was separated, washed with brine and concentrated under reduced pressure. The resulting solid was treated with HCl (2.0 M, 100 ml) and then evaporated to dryness under reduced pressure. Impurities precipitated out as a white solid, when the amine hydrochloride salt was dissolved in hot MeOH and allowed to cool to room temperature. After removing the impurities by filtration, the filtrate was made basic with KOH (1.0 M) and the organics were extracted into diethyl ether (4x100 ml). Combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure to obtain a crude product as a light brown solid. Purification over silica gel, eluting with a 1:4 and 1:1 mixture of ethyl acetate and petrol gave the title compound (2) (5.42 g, 36 %) as a white solid. m.p. 90-92 °C (lit[i] 94-95 °C). $[\alpha]_D^{25}$ = - 107.92° (c, 0.0424 in $CHCl_3$) (lit[ii]: - 127.7° (c, 0.639 in $CHCl_3$). δ_H 0.81 (3H, d, ^3J= 6.90 Hz, CH_3), 0.85 (3H, d, ^3J= 7.20 Hz), 1.67 (1H, ds, ^3J= 1.80 and 6.90 Hz, CH-Me_2), 3.76 (1H, d, ^3J= 2.10 Hz, CH-NH_2), 7.04-7.58 (10H, m, Ar). δ_C 16.3 and 23.2 (CH_3), 28.1 (CH-Me_2), 60.4 (CH-NH_2), 79.9 (C-OH), 125.7, 126.1, 126.5, 126.8, 128.2 and 128.6 (o-, m- and p-Ar), 145.1 and 148.2 (α-Ar). Anal. Calcld. for $C_{17}H_{21}NO$: C 79.96; H 8.29; N

5.48. Found: C 79.80; H 8.15; N 5.39. ir 3338 (OH and NH_2). m/e (CI-CH_4) 256 (MH^+, 14 %), 72 (100 %).

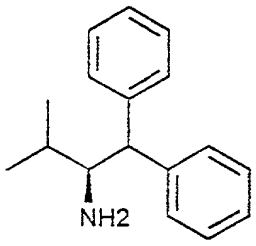
(S)-4-isopropyl-5,5-diphenyl-2-oxazolidinone (3)



(3)

Trichloromethyl chloroformate (2.71 g, 13.7 mmol) was added to a mixture of (S)-2-amino-3-methyl-1,1-diphenyl-1-butanol (2) (3.18 g, 12.45 mmol) and triethylamine (2.68 g, 26.52 mmol) in CH_2Cl_2 at 0 °C. The reaction mixture was stirred for 2h at the same temperature and then poured into a brine solution (250 ml). The aqueous layer was made basic with NaOH pellets and organic products were extracted into AcOEt (5x200 ml). Combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The resulting crude product was washed with diethyl ether to obtain the title compound (3) (3.03 g, 86 %) as a white solid. m.p. 250-251 °C (liti 250-251 °C). $[\alpha]_D^{25}$ = - 201.59° (c, 0.0252 in DMSO). δ_H (DMSO-d_6) 0.51 (3H, d, ^3J= 6.60 Hz, CH_3), 0.92 (3H, d, ^3J= 7.20 Hz, CH_3), 1.86 (1H, ds, ^3J= 2.10 and 6.60 Hz, CH-Me_2), 4.46 (1H, d, ^3J= 6.5 Hz, CH-NH_2), 7.24-7.72 (10H, m, Ar-H), 8.14 (1H, s, NH). δ_C 15.2 and 20.9 (CH_3), 29.8 (CH), 64.9 (CH-NHCO), 88.4 (C-O), 125.8, 126.2, 127.9, 128.4, 128.8 and 129.1 (Ar), 140.5 and 146.1 (α-Ar), 158.1 (C=O). Ir 3295 (NH_2), 1765 and 1745 (C=O). m/e (CI-NH_3) 282 (MH^+, 25 %), 299 (MNH_4^+, 8 %), 238 (96 %), 223 (100 %), 72 (100 %).

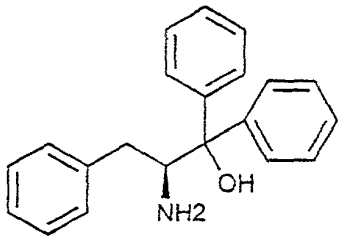
(S)-2-amino-3-methyl-1,1-diphenylbutane (4)



(4)

A solution of (S)-4-isopropyl-5,5-diphenyl-2-oxazolidinone (3) (2.9 g, 10.31 mmol) in MeOH/AcOH and a 10 % Pd (435 mg, 4.09 mmol) on activated carbon was shaken for 68h under 4-5 atm pressure of hydrogen at room temperature. The catalyst was filtered off over Hyflo Super Cell and organic solvents were evaporated under reduced pressure. The resulting residue was treated with HCl (2.0 M, 50 ml), stirred for 2h at room temperature, made basic with NaOH pellets, and saturated with K_2CO_3 and NaCl. Organic compounds were then extracted into AcOEt (3x 100 ml), dried over $MgSO_4/K_2CO_3$ and concentrated under reduced pressure to obtain a crude product. Re-crystallisation from petroleum ether gave the title compound (4) (1.79 g, 72 %) as a light-brown solid. m.p. 71-72 °C. $[\alpha]_D^{25} = -4.19°$ (c, 0.1097 in $CHCl_3$). δ_H 0.78 (3H, d, ^3J= 6.60 Hz. CH_3), 0.91 (3H, d, ^3J= 7.20 Hz, CH_3), 1.26 (2H, broad s, NH_2), 1.62 (1H, ds, $CHMe_2$), 3.45 (1H, dd, ^3J= 10.5 and 2.40 Hz, CH-NH_2), 3.70 (1H, d, ^3J= 10.5 Hz, CH-Ph_2), 7.00-7.40 (10H, m, Ar-H). δ_C 14.2 and 21.5 (CH3), 28.9 (CH-Me_2), 58.1 and 58.9 (CH-NH_2 and CH-Ph_2), 126.5, 126.7, 128.2, 128.5, 128.8 and 129.0 (o-, m- and p-Ar), 143.5 (2xα-Ar). Anal. Calcld for $C_{17}H_{21}N$: C 85.30; H 8.84; N 5.85. Found: C 85.12; H 8.91; N 5.96. ir 3361 (NH_2). m/e (CI-CH_4) 240 (MH^+, 8 %), 72 (100 %).

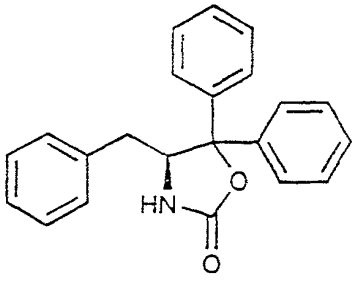
1.2 (S)-2-Amino-1,1,3-triphenyl-1- propanol (6)



(6)

L-Phenylalanine ethyl ester hydrochloride (9.9 g, 43.1 mmol) was added portionwise to a 1.0 M solution of phenylmagnesium bromide (63.46 g, 0.35 mol) in THF at 0 °C and stirred for 20h at room temperature. After quenching with crushed ice and concentrated HCl, the aqueous layer was separated and evaporated to dryness under reduced pressure. The resulting solid was washed with diethyl ether and AcOEt to obtain a white gummy HCl-salt. Upon basification with NaOH (1.0 M), organic products were extracted into diethyl ether and AcOEt, dried over $MgSO_4$, and concentrated under reduced pressure to obtain a crude product. Re-crystallisation from a mixture of AcOEt and diethyl ether gave the title compound (6) (1.16 g, 9 %) as a white solid. m.p. 141-142 °C (lit[ii] 144-145 °C; lit[vi] 143-144 °C). $[\alpha]_D^{25}$ = - 88.40° (c, 0.0181 in $CHCl_3$) (lit[ii]: - 88.50° (c, 0.604 in $CHCl_3$); lit[vi]: - 94.3° (c, 2.30 in $CHCl_3$). δ_H 2.38 (1H, dd, ^3J= 10.8 Hz, ^2J= 13.8 Hz, CH_2-Ph), 2.58 (1H, dd, ^3J= 2.4 Hz, ^2J= 13.8 Hz, CH_2-Ph), 4.11 (1H, dd, ^3J= 2.4 Hz, ^3J= 10.8 Hz, CH-NH_2), 7.06-7.62 (15H, m, Ar-H). δ_C 36.9 (CH_2-Ph), 58.4 (CH-NH_2), 78.7 (C-OH), 125.6, 126.0, 126.6, 126.7, 126.9, 128.4, 128.7, 128.8 and 129.3 (o-, m- and p-Ar), 139.8, 144.5 and 147.0 (α-Ar). ir 3365 (NH_2), 3320 (OH). m/e (CI-NH_3) 304 (MH^+, 30 %), 271 (100 %).

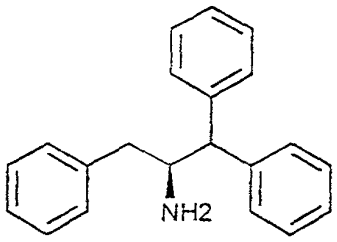
(S)-4-benzyl-5,5-diphenyl -2- oxazolidinone (7)



(7)

Trichloromethyl chloroformate (718 mg, 3.63 mmol) was added to a mixture of (S)-2-amino-1,1,3-triphenyl-1-propanol (6) (1.00 g, 3.30 mmol) and triethylamine (710 mg, 7.02 mmol) in CH_2Cl_2 at 0 °C. The reaction mixture was stirred for 5h at the same temperature and then poured into a brine solution (150 ml). The aqueous layer was made basic with powdered K_2CO_3 and organics were extracted into dichloromethane (3x50 ml). The combined organic extracts were dried over $MgSO_4/K_2CO_3$ and concentrated under reduced pressure. The resulting crude product was washed with diethyl ether to obtain the title compound (7) (1.06 g, 97 %) as a white solid. m.p. 259-261 °C (lit ? °C). $[\alpha]_D^{25}$ = -241.94° (c, 0.0211 in DMSO), δ_H (DMSO-d_6) 2.18 (1H, dd, ^3J= 10.8 Hz, ^2J= 13.8 Hz, CH_2-Ph), 2.52 (1H, dd, ^3J= 3.6 Hz, ^2J= 13.8 Hz, CH_2-Ph), 4.67 (1H, dd, ^3J= 3.6 Hz, ^3J= 10.8 Hz, CH-NH_2), 6.90-7.60 (15H, m, Ar-H). δ_C 44.2 (CH_2-Ph), 50.5 (CH-NH), 94.1 (C-O), 130.5, 130.9, 131.5, 132.6, 132.8, 133.0, 133.1, 133.3 and 133.4 (o-, m- and p-Ar), 141.1, 143.4 and 146.5 (α-Ar), 163.7 (C=O). ir 3248 (NH_2), 1760 and 1725 (C=O). m/e (CI-NH_3) 330 (MH^+, 5 %), 347 (MNH_4^+, 6 %), 196 (100 %).

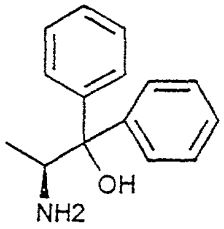
(S)-2-Amino-1,1.3-triphenyl-propane (8)



(8)

A solution of (S)-4-benzyl-5,5-diphenyl-2-oxazolidinone (7) (940 mg, 2.85 mmol) in MeOH/AcOH and a 10 % Pd (121 mg, 1.14 mmol) on activated carbon was shaken for 43h under 4-5 atm pressure of hydrogen at room temperature. The catalyst was filtered off over Hyflo Super Cell and organic solvents were evaporated under reduced pressure. The resulting residue was treated with HCl, stirred for 2h at room temperature, made basic with NaOH pellets, and saturated with K_2CO_3 and NaCl. Organics were then extracted into dichloromethane (4x 50 ml), dried over $MgSO_4/K_2CO_3$ and concentrated under reduced pressure to obtain a crude product. Purification over silica gel, eluting with a 3:7 and 4:6 mixture of AcOEt and petroleum ether, gave the title compound (8) (584 mg, 71 %) as a light-brown solid. m.p. 71-72 °C. $[\alpha]_D^{25}$ = -8.03° (c, 0.1046 in $CHCl_3$). δ_H 1.21 (2H, broad s, NH_2), 2.29 (1H, dd, ^3J= 9.6 Hz, ^2J= 13.5 Hz, CH_2-Ph), 2.79 (1H, dd, ^3J= 2.1 Hz, ^2J= 13.2 Hz, CH_2-Ph), 3.71 (1H, d, ^3J= 9.9 Hz, CH-Ph_2), 3.81 (1H, ddd, ^3J= 2.7, 9.9 and 12.6 Hz, CH-NH_2), 7.06-7.33 (15H, m, Ar-H). δ_C 41.9 (CH_2-Ph), 55.7 and 59.7 (CH-Ph_2 and CH-NH_2), 126.3, 126.5, 126.6, 128.1, 128.2, 128.4, 128.7, 128.8 and 129.1 (o-, m- and p-Ar), 139.7, 142.6 and 143.1 (α-Ar). ir 3387 (NH_2). m/e (CI-NH_3) 288 (MH^+, 100 %).

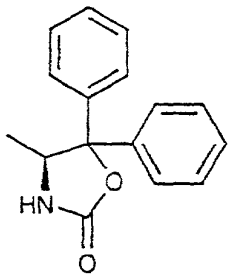
1.3 (S)-2-Amino-1,1-diphenyl-1- propanol (10)



(10)

L-Alanine methyl ester hydrochloride (9.9 g, 70.9 mmol) was added portionwise to a 1.0 M solution of phenylmagnesium bromide (78.0 g, 0.43mol) in THF at 0 °C and then heated under reflux for 21h. The reaction mixture was cooled to 0 °C, quenched with dropwise addition of saturated NH_4Cl, and stirred for 1h. After collecting insoluble products through the Buchner funnel, organic products were extracted into AcOEt (3x100 ml). The combined organic extracts were dried over $K_2CO_3/MgSO_4$, and concentrated under reduced pressure to obtain a crude product. Impurities were washed with dichloromethane over silica gel by means of dry-flash column chromatography, further elution with a mixture of AcOEt and petrol, ranging from 20 % up to100 %, gave the title compound **(10)** (1.16 g, 9 %) as a white solid. m.p. 100-101 °C (lit[ii,v] 100-102 °C). $[\alpha]_D^{25} = -85.59°$ (c, 0.0362 in $CHCl_3$) (lit[ii]: -82.38° (c, 0.814 in $CHCl_3$; lit[v]: -85.9° (c, 2.77 in $CHCl_3$). δ_H 0.94 (3H, d, ^3J= 6.30 Hz, CH_3), 1.23 (2H, broad s, NH_2), 4.15 (1H, q, ^3J= 6.30 Hz, CH-NH_2), 4.25 (1H, broad s, OH), 7.10-7.66 (10H, m, Ar-H). δ_C 17.4 (CH_3), 52.1 (CH-NH_2), 78.7 (C-OH), 125.7, 126.1, 126.6, 126.9, 128.2 and 128.7 (o-, m- and p-Ar), 145.0 and 147.2 (α-Ar). Anal. Calcld. for $C_{15}H_{17}NO$: C 79.26; H 7.54; N 6.16. Found: C 79.30; H 7.66; N 6.27. ir 3432 (OH), 3389 (NH_2). m/e (CI-NH_3) 228 (MH^+, 100 %).

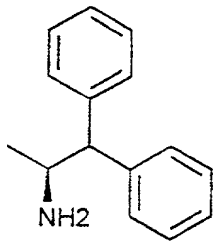
(S)-4-Methyl-5,5-diphenyl-2-oxazolidinone (11)



(11)

Trichloromethyl chloroformate (6.37 g, 32.19 mmol) was added to a mixture of (S)-2-amino-1,1-diphenyl-1-propanol **(10)** (6.65 g, 29.26 mmol) and triethylamine (6.31 g, 62.3 mmol) in CH_2Cl_2 at 0 °C. The reaction mixture was stirred for 5h at the same temperature, poured into a brine solution (150 ml), and diluted with more dichloromethane. After collecting insoluble impurities through the Buchner funnel, the organic layer was separated and the aqueous layer was washed once with a mixture of dichloromethane and AcOEt. The combined organic extracts were dried over $MgSO_4/K_2CO_3$ and concentrated under reduced pressure. The resulting crude product was washed with diethyl ether, water, AcOEt and diethyl ether again, to obtain the title compound **(11)** (5.67 g, 76 %) as a white solid. m.p. 264-266 °C $[\alpha]_D^{25}$ = -279.71° (c, 0.0414 in DMSO). δ_H 0.82 (3H, d, ^3J= 6.30 Hz, CH_3), 4.65 (1H, q, ^3J= 6.0 Hz, CH-NH_2), 7.10-7.70 (10H, m, Ar-H), 7.93 (1H, broad s, NH). δ_C 19.6 (CH_3), 55.9 (CH-NH_2), 85.6 (C-O), 126.3, 126.4, 128.1, 128.6, 128.8 and 129.1 (o-, m- and p-Ar), 140.6 and 144.2 (α-Ar), 157.6 (C=O). ir 3254(NH), 1745 and 1725 (C=O). m/e (CI-NH_3) 254 (MH^+, 9 %), 271 (MNH_4^+, 55 %), 52 (100 %).

(S)-2-Amino-1,1-diphenyl-propane (12)

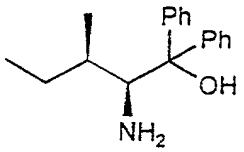


(12)

A suspension of (S)-4-methyl-5,5-diphenyl-2-oxazolidinone (11) (3.52 g, 13.90 mmol) in MeOH/AcOH and a 10 % Pd (148 mg, 1.39 mmol) on activated carbon was shaken for 45h under 4-5 atm pressure of hydrogen at room temperature. The catalyst was filtered off over Hyflo Super Cell and organic solvents were evaporated under reduced pressure. The resulting residue was treated with HCl (2M, 100 ml), stirred overnight at room temperature, made basic with NaOH pellets, and saturated with K_2CO_3. The organics were then extracted into diethyl ether (3x 100 ml), dried over $MgSO_4/K_2CO_3$ and concentrated under reduced pressure to obtain a crude product. Impurities were washed with AcOEt over silica gel by means of dry-flash column chromatography, and then further elution with a mixture of MeOH and AcOEt, ranging from 5 % up to 30 %, gave the title compound (12) (1.90 g, 65 %) as a white solid. m.p. 76-77 °C. $[\alpha]_D^{25}$ = - 19.32 (c, 0.10765 in $CHCl_3$). δ_H 1.04 (3H, d, ^3J= 6.30 Hz, CH_3), 1.31 (2H, broad s, NH_2), 3.55 (1H, d, J= 9.90 Hz, CH-Ph_2), 3.73 (1H, dq, ^3J= 6.30 and 10.20 Hz, CH-NH_2), 7.10-7.40 (10H, m, Ar-H). δ_C 22.4 (CH_3), 50.3 (CH-NH_2), 62.4 (CH-Ph_2), 126.5, 126.8, 128.2, 128.5, 128.7 and 129.0 (o-, m- and p-Ar), 143.3 and 143.7 (α-Ar). Anal. Calcld for $C_{15}H_{17}NO$: C 85.26; H 8.11; N 6.63. Found: C 85.10; H 8.08; N 6.36. ir 3343 (NH_2). m/e (CI-NH_3) 212 (MH^+, 100 %).

1.4 (*S*)-α-(Diphenylmethyl)-α-[(*R*)-1-methylpropyl)-methylamine (15)

(*2S,3R*)-2-Amino-1,1-diphenyl-3-methylpentan-1-ol (13)

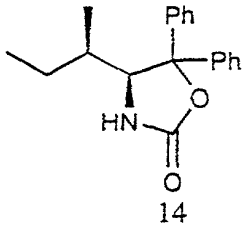


13

A 1 M solution of phenylmagnesium bromide (49.0 g, 0.27 mol) in THF was added dropwise to (*S*)-isoleucine methyl ester hydrochloride (9.8 g, 54.0 mmol) at 0 °C and then stirred for 17h at room temperature. The reaction mixture was cooled to 0 °C, quenched with dropwise addition of saturated NH_4Cl and then diluted with AcOEt and water until partition occurred. Organic products were extracted into AcOEt (3x50 ml), dried over $MgSO_4/K_2CO_3$ and concentrated to obtain a crude product. The crude product was dissolved in diethyl ether (150 ml), treated with concentrated HCl until all of the amine was converted to its HCl salt. The amine-HCl salt was stirred overnight, diluted with water until partition occured. The non-basic organics were extracted into diethyl ether (5x100 ml) and then the aqueous layer was made basic with NaOH pellets. After stirring for 4h, organic products were extracted into AcOEt (4x75 ml) and dried over $MgSO_4/K_2CO_3$. Concentration gave a crude product (6.1 g, 42 %) as a pale yellow solid. This contaminated with the amino ester derived from the starting material, however was used for the next step without further purification. A small amount of the crude product (1.1 g) was purified over silica gel by means of dry-flash column chromatography, eluting first with CH_2Cl_2, then with a mixture of AcOEt and petrol, increasing from 40 % up to 80 %. From this, a pure amino alcohol 13 (654 mg, 60 %) was obtained as a white amorphous solid. **m.p.** 128-129 °C (lit 135-136 °C). $[\alpha]_D^{25}$ = - 128.17° (c, 4.26 in $CHCl_3$) (lit: - 124.1° (c, 1.23 in $CHCl_3$)). δ_H 0.72 (3H, t, J= 7.2 Hz, CH_3), 0.94 (3H, d, J= 6.9 Hz, CH_3), 0.80-1.10 (1H, m, CH_2), 1.40-1.60 (1H, m, CH), 1.76-1.94 (1H, m, CH_2), 0.60-2.10 (3H, OH and NH_2), 3.85 (1H, d, J= 1.5 Hz, CH-NH_2), 7.10-7.70 (10H, m, Ar-H). δ_C 12.1 (CH_3-CH_2), 18.7 (CH_3-CH), 22.5 (CH_2), 34.8 (CH-Me), 60.9 (CH-NH_2), 79.6 (C), 125.5, 125.9, 126.1, 126.5, 127.8, 128.2,

144.9, 147.9 (Ar). ν_{max} (cm^{-1}): 3343, 3279 (N-H and O-H), 3085, 3023 (Ar C-H), 2959, 2926, 2873 (methyl and methylene C-H), 1589, 1491, 1447 (Ar C=C). m/e 270 (MH^+, 4 %), 252 (20 %), 86 (100 %).

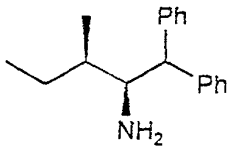
(*S*)-4-[(R)-1-Methylpropyl]-5,5-diphenyl-2-oxazolidinone 14



14

Trichloromethyl chloroformate (5.4 g, 27.3 mmol) was added to a mixture of (*S*)-2-amino-1,1-diphenyl-3-methylpentan-1-ol **13** (4.97 g of 60 %, 11.1 mmol) and triethylamine (5.3 g, 52.0 mmol) in CH_2Cl_2 at 0 °C. The reaction mixture was stirred for 3h at 0 °C, then allowed to warm to room temperature for 18h. The mixture was then washed with HCl (3x100 ml) and water (2x100 ml) and dried over $MgSO_4$. Concentration gave a crude product, which was washed with diethyl ether to afford the title compound **14** (2.7 g, 83 %) as a white amorphous solid. **m.p.** 221-223 °C. $[\alpha]_D^{25}$ = - 243.9° (c, 4.33 in $CHCl_3$). δ_H 0.41 (3H, t, J= 7.2 Hz, CH_3), 0.80 (3H, d, J= 6.9 Hz, CH_3), 0.80-0.96 (1H, m, CH_2), 1.18-1.32 (1H, m, CH-Me), 1.34-1.50 (1H, m, CH_2), 4.27 (1H, d, J= 3.6 Hz, CH-NH), 6.98 (1H, s, NH), 7.10-7.50 (10H, m, Ar-H). δ_C 11.3 (CH_3-CH_2), 17.2 (CH_3-CH), 22.7 (CH_2), 36.3 (CH-Me), 66.1 (CH-NH), 89.5 (C), 125.9, 126.5, 127.7, 128.0, 128.3, 128.6, 139.3, 144.0 (Ar), 159.1 (C=O). ν_{max} (cm^{-1}): 3281, 3162 (N-H), 3058 (Ar C-H), 2980, 2960, 2933, 2877 (methyl and methylene C-H), 1760, 1725 (C=O), 1493, 1448 (Ar C=C), 1243 (C-O). m/e 313 (MNH_4^+, 6 %), 296 (MH^+, 8 %), 237 (100 %).

(*S*)-α-(Diphenylmethyl)-α-[(*R*)-1-methylpropyl)-methylamine 15

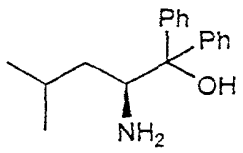


15

A suspension of (*S*)-4-*sec*-butyl-5,5-diphenyl-2-oxazolidinone 17 (2.3 g, 7.9 mmol) in MeOH/AcOH and a 10 % Pd (100 mg, 0.9 mmol) on activated carbon was shaken for 47h under 4-5 atm pressure of hydrogen at room temperature. The catalyst was filtered off over Hyflo Super Cell and solvents were evaporated. The resulting residue was treated with HCl until all of the amine was converted to its HCl salt, stirred overnight at room temperature and diluted with water until partition occurred. The non-basic organics were extracted into diethyl ether (2x100 ml) and the aqueous layer was made basic with NaOH pellets. Organic compounds were then extracted into CH_2Cl_2 (5x100 ml) and the combined extracts were dried over $MgSO_4$. Concentration gave a crude product, which was purified over silica gel by means of dry-flash column chromatography, eluting first with CH_2Cl_2, then with a mixture of AcOEt and petrol, ranging from 50 % up to 70 %. This afforded the title compound **15** (1.4 g, 71 %) as a white amorphous solid. **m.p.** 59-61 °C. $[\alpha]_D^{25} = -13.7°$ (c, 4.80 in $CHCl_3$). δ_H 0.76 (3H, t, J= 7.5 Hz, CH_3), 0.96 (3H, d, J= 6.9 Hz, CH_3), 1.00-1.18 (3H, broad s and m, NH_2 and CH_2), 1.28-1.42 (1H, m, CH-Me), 1.50-1.70 (1H, m, CH_2), 3.50 (1H, dd, J= 10.5 and 2.40 Hz, CH-NH_2), 3.87 (1H, d, J= 10.5 Hz, CH-Ph_2), 7.10-7.40 (10H, m, Ar-H). δ_C 11.2 (CH_3-CH_2), 16.7 (CH_3-CH), 20.4 (CH_2), 34.8 (CH-Me), 56.4 (CH-Ph_2), 58.4 (CH-NH_2), 125.2, 125.4, 127.0, 127.4, 127.5, 127.7 (Ar). **Accurate mass (CI):** Found 254.189998; Calculated for (MH^+) $C_{18}H_{24}N$ 254.190875 (3.4 ppm). ν_{max} (**cm**$^{-1}$): 3355 (N-H), 3082, 3065, 3024 (Ar C-H), 2959, 2931, 2872 (methyl and methylene C-H), 1598, 1494, 1450 (Ar C=C). **m/e (CI)** 254 (MH^+, 100 %).

1.5 (*S*)-α-(Diphenylmethyl)-α-isobutyl-methylamine 18

(*S*)-2-Amino-1,1-diphenyl-4-methylpentan-1-ol

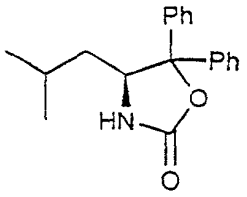


16

A 1 M solution of phenylmagnesium bromide (96.1 g, 0.53 mol) in THF was added dropwise at 0 °C to (*S*)-leucine methyl ester hydrochloride (19.3 g, 0.11 mol) and then stirred for 17h at room temperature. The reaction mixture was cooled to 0 °C, quenched with dropwise addition of saturated NH_4Cl and then diluted with AcOEt and water until partition occurred. Organic products were extracted into AcOEt (3x100 ml), dried over $MgSO_4/K_2CO_3$ and concentrated to obtain a crude product. The crude product was dissolved in diethyl ether (400 ml), treated with concentrated HCl until all of the amine was converted to its HCl salt. The amine-HCl salt was stirred overnight and then diluted with water until partition occurred. The non-basic organics were extracted into diethyl ether (5x100 ml) and then the aqueous layer was made basic with NaOH pellets. After stirring for 4h, organic products were extracted into AcOEt (4x200 ml) and dried over $MgSO_4/K_2CO_3$. Concentration gave a crude product (13.7 g, 48 %) as a pale yellow solid. This contaminated with the amino ester of the unreacted starting material, however was used directly for the next step without further purification. A small amount of the crude product (1.31 g) was purified over silica gel by means of dry-flash column chromatography, eluting first with CH_2Cl_2, then a mixture of AcOEt and petrol, increasing from 30 % up to 55 %. From this, a pure amino alcohol **16** (852 mg, 65 %) was obtained as a white amorphous solid. **m.p.** 131-132 °C (lit 132-134 °C). $[\alpha]_D^{25} = -101.0°$ (c, 5.38 in $CHCl_3$) (lit: -95.1° (c, 1.01 in $CHCl_3$)). δ_H 0.79 (6H, dd, J= 7.20 and 7.80 Hz, CH_3), 0.86-1.80 (6H), 3.89 (1H, J= 9.6 Hz, CH-NH_2), 7.00-7.70 (10H, m. Ar-H). δ_C 21.1, 23.8, 25.1, 39.2, 54.3. 78.9, 125.4. 125.6, 126.1, 126.4, 127.8, 128.2. 144.3, 147.0 (Ar). ν_{max} (cm^{-1}): 3337, 3268 (N-H and O-H), 3025 (Ar C-H), 2954, 2935, 2866 (methyl and methylene C-H), 1597, 1491, 1448 (Ar C=C). **m/e** 270 (MH^+, 5 %), 252 (M-OH, 11 %), 86 (100 %).

(*4S*)-4-Isobutyl-5,5-diphenyl-2-oxazolidinone 17

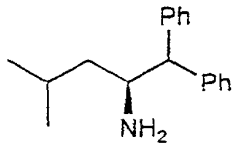
29



17

Trichloromethyl chloroformate (13.0 g, 65.8 mmol) was added to a mixture of (S)-2-amino-1,1-diphenyl-4-methylpentan-1-ol **16** (12.4 g of 65 %, 29.9 mmol) and triethylamine (12.7 g, 125.5 mmol) in CH_2Cl_2 at 0 °C. The reaction mixture was stirred for 15h, allowing to warm to room temperature. The mixture was then washed with HCl (3x200 ml) and water (2x200 ml), and dried over $MgSO_4$. Concentration gave a crude product, which was washed with diethyl ether to afford the title compound **17** (7.9 g, 90 %) as a white solid. **m.p.** 212-214 °C. $[\alpha]_D^{25} = -286.1°$ (c, 4.32 in $CHCl_3$). δ_H 0.85 (3H, d, J= 6.6 Hz, CH_3), 0.91 (3H, d, J= 6.6 Hz, CH_3), 0.96-1.08 (2H, m, CH_2), 1.53-1.73 (1H, m, CH-Me_2), 4.57 (1H, dd, J= 10.5 and 3.60 Hz, CH-NH), 7.05 (1H, s, NH), 7.16-7.50 (10H, m, Ar-H). δ_C 20.8, 23.7, 24.9, 41.8, 58.8, 89.1, 125.9, 126.3, 127.6, 127.8, 128.1, 128.3, 139.3, 142.5 (Ar), 158.8 (C=O). ν_{max} **(cm-1):** 3261, 3160 (N-H), 2955, 2869 (methyl and methylene C-H), 1752, 17235 (C=O), 1495, 1447 (Ar C=C), 1251 (C-O). **m/e** 313 (MNH_4^+, 12 %), 296 (MH^+, 15 %), 237 (100 %).

(*S*)-α-(Diphenylmethyl)-α-isobutyl-methylamine 18



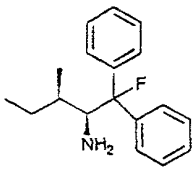
18

A suspension of (*S*)-4-isobutyl-5,5-diphenyl-2-oxazolidinone **17** (7.6 g, 25.6 mmol) in MeOH/AcOH and a 10 % Pd (282 mg, 2.6 mmol) on activated carbon was shaken for 93h under 4-5 atm pressure of hydrogen at room temperature. The catalyst was filtered off over Hyflo Super Cell and solvents were evaporated under reduced pressure. The resulting residue was treated with HCl until all of the amine was converted to its HCl salt, stirred overnight at room temperature and diluted with water until partitioned occurred. The non-basic organics were extracted into diethyl

ether (2x100 ml) and then the aqueous layer was made basic with NaOH pellets. Organics were then extracted into CH_2Cl_2 (5x 100 ml) and the combined extracts were dried over $MgSO_4$. Concentration gave the title product **18** (5.7 g, 87 %) as a white amorphous solid. **m.p.** 46-48 °C.. $[\alpha]_D^{25}$ = -31.6° (c, 4.12 in $CHCl_3$). δ_H 0.86 (6H, dt, J= 6.60 and 2.10 Hz, CH_3), 1.00-1.50 (4H, m and broad s, CH_2 and NH_2), 1.66-1.86 (1H, m, CH), 3.61 (2H, broad s, CH-NH_2 and CH-Ph_2), 7.10-7.40 (10H, m, Ar-H). δ_C 21.8 and 24.7 (CH_3), 25.5 (CH), 45.6 (CH_2), 52.4 (CH-NH_2), 61.6 (CH-Ph_2), 126.9, 127.1, 128.8, 129.0, 129.2, 129.4, 143.8, 144.0 (Ar). **Accurate mass (CI):** Found 254.190200; Calculated for (MH^+) $C_{18}H_{24}N$ 254.190875 (2.7 ppm). ν_{max} **(cm^{-1}):** 3368 (N-H), 3057, 3027 (Ar C-H), 2951, 2932, 2909, 2867 (methyl and methylene C-H), 1595, 1494, 1450 (Ar C=C). **m/e (CI)** 254 (MH^+, 100 %).

2. Chiral Amines wherein Z is F

2.1 (*S*)-α-(Fluorodiphenylmethyl)-α-[(*R*)-1-methylpropyl)-methylamine 19



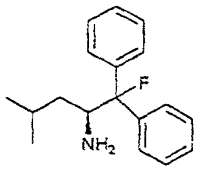
19

A solution of the oxazolidinone **14** (100mg, 0.34mmol) in CH_2Cl_2 (5ml) was carefully added to 30% HF-pyridine (2ml) (Olah's reagent) in a polythene bottle, and the contents were cooled to 0^{0}C. The solution was allowed to reach ambient temperature over 24 hours and was then poured into ice-cooled 2N aqueous ammonia solution (50ml). The organic layer was separated and the aqueous layer extracted into CH_2Cl_2 (3 x 30ml). The combined organic layers were dried over $MgSO_4$ and were then filtered and the solvent removed under reduced pressure. Purification by flash-column over silica gel chromatography (eluting with EtOAc/PetEt 1:4) generated the

fluorinated amine 19 as a white amorphous solid (23.1mg, 25%). On the basis of recovered starting material the yield is corrected to 53%.

$[\alpha]_D$=-32.3°(MeOH, c = 0.6), m.p.: 76.9°C; δ_H (400 MHz; $CDCl_3$): 7.45-7.16 (10H, m, $CH_{ar.}$), 3.82 (1H, qd, *J* 25.60 and 6.40, C**H**-NH_2), 1.65 (2H, s, NH_2), 1.03 (3H, *J* 6.80, CH_3); δ_F (376 MHz; $CDCl_3$): -174.91 (d, *J* 24.46)
HRMS (CI, M+H^+) found 272.1814. $C_{18}H_{22}NF$ requires 272.1815.

2.2 (*S*)-α-(Fluorodiphenylmethyl)-α-isobutyl-methylamine 20

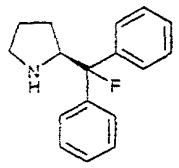


20

A solution of the oxazolidinone **16** (150mg, 0.51mmol) in CH_2Cl_2 (5ml) was carefully added to 30% HF-pyridine (1.5ml) (Olah's reagent) in a polythene bottle, and the contents were cooled to 0°C. The solution was allowed to reach ambient temperature over 24 hours and was then poured into ice-cooled 2N aqueous ammonia solution (50ml). The organic layer was separated and the aqueous layer extracted into CH_2Cl_2 (3 x 30ml). The combined organic layers were dried over $MgSO_4$ and were then filtered and the solvent removed under reduced pressure. Purification by flash-column over silica gel chromatography (eluting with EtOAc/CH_2Cl_2, 1:4) generated the fluorinated amine 14 as a white amorphous solid (61mg, 44%). On the basis of recovered starting material the yield is corrected to 61%.

$[\alpha]_D$=-48.78°(MeOH, c= 1.2); m.p.: 84°C; δ_H (400 MHz; $CDCl_3$): 7.50-7.26 (10H, m, CH_{ar}), 3.72 (1H, ddd, *J* 26.0, 10.4 and 2.0, C**H**-NH_2), 1.85 (1H, m, C**H**$(CH_3)_2$), 1.51 (2H, s, NH_2), 1.35 (1H, m, CH_aH_b), 1.18 (1H, m, CH_aH_b), 0.87 (6H, t, *J* 6.4, 2CH_3; δ_F (376 MHz; $CDCl_3$): -174.1 (d, *J* 30.12); m/z (EI): 251 (5%, M-HF), 208 (26, [M-HF]-$CH(CH_3)_2$), 194 (8, [M-HF]-$CH_2CH(CH_3)_2$); HRMS (CI, M+H^+) found 272.1812. $C_{18}H_{22}NF$ requires 272.1815.

2.3 (S)-2-(Fluorodiphenylmethyl)-pyrrolidine 21



21

A solution of the oxazolidinone (200mg, 0.7mmol) in CH_2Cl_2 (5ml) was carefully added to 30% HF-pyridine (2ml) (Olah's reagent) in a polythene bottle, and the contents were cooled to 0^0C. The solution was allowed to reach ambient temperature over 24 hours and was then poured into ice-cooled 2N aqueous ammonia solution (50ml). The organic layer was separated and the aqueous layer extracted into CH_2Cl_2 (3 x 30ml). The combined organic layers were dried over $MgSO_4$ and were then filtered and the solvent removed under reduced pressure. Purification by flash-column over silica gel chromatography (eluting with EtOAc/petrol, 6:4) generated the fluorinated amine 14 and a viscous oil (55.8mg, 31%).

$[\alpha]_D$ = -8.08° (MeOH, c 7.4), δ_H (400 MHz; $CDCl_3$): 7. 47-7.16 (10H, m, $CH_{ar.}$), 4.14 (1H, td, *J* 28.40 and 7.20, **CH**), 3.02-2.95 (1H, m, CH_AH_B-NH), 2.85-2.77 (1H, m, CH_AH_B-NH), 1.81-1.20 (2H, m, **NH** and $2CH_2$); δ_F (376 MHz; $CDCl_3$): -171.02 (d, *J* 27.47). m/z (CI): 256 (76%, M+1), 236 (100, [M-HF]+1); HRMS (C1, $M+H^+$) found 256.1499. $C_{17}H_{18}NF$ requires 256.1502.

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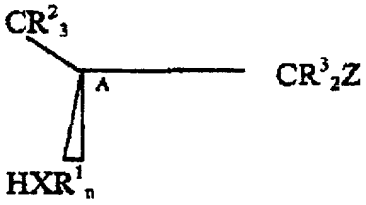
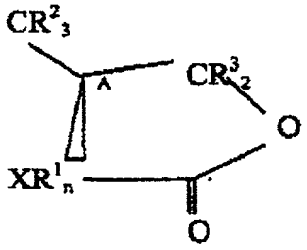
CLAIMS

1. Process for the preparation of enantiomerically pure compounds of formula I:

(I) 

comprising contacting a compound of formula II:

(II) 

with a source of hydrogen at ambient temperature and elevated pressure in the range 1 – 10 atm for a period *which is other than 2 hours or less (proviso taking basis from D3); alternatively for a period of 43 hours (taking basis from Examples); alternatively for a period in the range 43 to 93 hours (taking basis from examples)* in the presence of a hydrogenation catalyst which is homogeneous or heterogeneous and comprises a metal selected from the transition metals of Group VIII of the Periodic Table of the Elements and a catalytic support; or

with a source of fluorine as a fluorination agent which comprises gaseous or liquid phase HF and a carrier, at temperature in the range 0 – 20C and ambient pressure for a period of 24 hours

wherein A is an *enantiomerically pure* centre *CH*; Z is hydrogen or *fluoro*

X is selected from oxygen, sulphur and nitrogen and n is selected from 0 and 1 and is equal to the valence of X less 2; and R^1 to R^3 are as defined below

and wherein each R^1 is independently selected from hydrogen or from straight chain or branched, saturated or unsaturated C_{1-8} hydrocarbon optionally substituted by one or more hydroxy, halo, aryl, cyclo C_{1-8} alkyl;

each R^3 is independently selected from hydrogen or halo; and straight and branched chain, saturated and unsaturated C_{1-4} alkyl, alkenyl and alkynyl and aryl;
each optionally substituted by hydroxy, halo, saturated or unsaturated C_{1-4} alkyl, alkenyl or alkynyl, aryl, cyclo C_{1-6} alkyl, carbonyl, carboxyl, amino, amido;

each R^2 is independently selected from hydrogen, straight chain and branched, saturated and unsaturated C_{1-8} alkyl, optionally substituted by hydroxy, halo, aryl, cyclo C_{1-6} alkyl, carbonyl, carboxyl, amino, amido.

2. Process as claimed in Claim 1 wherein X is nitrogen whereby n is 1.

3. Process as claimed in any one of Claims 1 and 2 wherein R^3 is selected from ethenyl, ethynyl and optionally substituted phenyl.

4. Process as claimed in any one of Claims 1-3 wherein at least one and preferably both of R^3 are aryl.

5. Process as claimed in any one of Claims 1-4 wherein R^2 is selected from optionally hydroxy, halo or alkoxy substituted branched and straight chain C_{1-6} alkyl, including methyl, ethyl, i-propyl, i-butyl, t-butyl; and aryl including phenyl and benzyl.

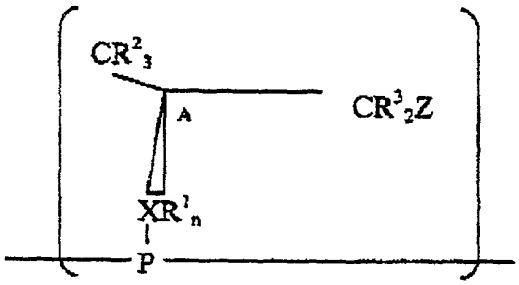
6. Process as claimed in any one Claims 1 to 5 wherein X is nitrogen wherein n is 1 and R^1 is H, i.e. the compound is a primary amine.

7. Process as claimed in any one of Claims 1-6 wherein a catalyst comprises Pd with C as catalytic support.

8. Process as claimed in any of Claims 1-7 wherein a fluorination agent is liquid phase HF-pyridine.

9 [13,14[16,17]]. *Process for preparation of a compound of the formula I as hereinbefore defined in any of Claims 1 to 8 which is a process for the* preparation of enantiomerically pure enantiomerically pure polymer comprising a repeating unit of the formula Ii:

(Ii)

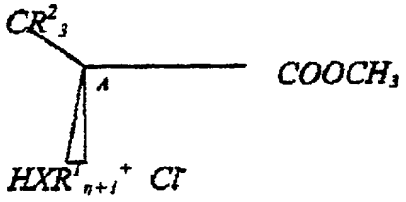


wherein P is derived from a polymerisable monomer or oligomer and X, R^1, R^2, R^3, Z and A are as hereinbefore defined in any of Claims 1 to 6; and

wherein a polymerisable monomer is selected from the group consisting of: an epoxy resin; an addition-polymerisation resin; a formaldehyde condensate resin; a cyanate resin; and an isocyanate resin; polyaromatics; monomers of natural polymers including carbohydrates, polypeptides and proteins including starch, celluloses, collagen, gelatin, dextrans, alginates, chitin and chitosan; and monomers of biodegradeable and/or biocompatible polymers including poly(lactic acid), poly(glycolic acid), polycaprolactone, polyorthoesters, polyanhydrides, polyaminoacids and azo polymers; and mixtures thereof.

10 [17,18[20,21]]. *Process for preparation of enantiomerically pure compounds of formula I as hereinbefore defined in any of Claims 1 to 8 which is a process for the* preparation of a library of compounds comprising:

reacting one or more compounds of formula IV

(IV) 

Wherein *R^1, R^2 and A are as hereinbefore defined in any of Claims 1 to 6*

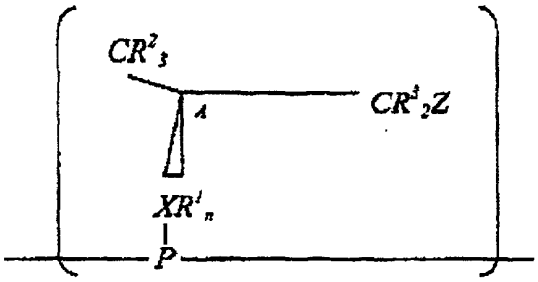
with a plurality of compounds of formula V R^2MgBr, and converting via compounds of formula II as hereinbefore defined *in Claim 1 to 6* to compounds of formula I as hereinbefore defined *in any of Claims 1 to 6*; and

optionally labelling the support or vessel with means to identify the synthetic history of the supported or contained compound.

11 [12]. *Enantiomerically pure* compound of the formula I as hereinbefore defined in any of Claims 1 to 6 wherein A, Z and R^1 to R^3 are as hereinbefore defined, X is N and n is 1.

12 [15[18]]. *Enantiomerically pure polymer comprising a repeating unit of the formula Ii:*

(Ii)



wherein *P is derived from a polymerisable monomer or oligomer selected from the group consisting of: an epoxy resin; an addition-polymerisation resin; a formaldehyde condensate resin; a cyanate resin; and an isocyanate resin; polyaromatics; monomers of natural polymers including carbohydrates, polypeptides and proteins including starch, celluloses, collagen, gelatin, dextrans, alginates, chitin and chitosan; and monomers of biodegradeable and/or biocompatible polymers including poly(lactic acid), poly(glycolic acid), polycaprolactone, polyorthoesters; and*

X, R^1, R^2, R^3, Z and A are as hereinbefore defined in any of Claims 1 to 6.

13 [19 [22]]. Library of enantiomerically pure compounds of formula I as hereinbefore defined *in Claim 11*.

14 [20 [23]]. Pharmaceutical, veterinary product or agrochemical composition comprising an enantiomerically pure compound of formula I, Ii or Iii as hereinbefore defined *in any of Claims 11 - 13* with suitable diluents, adjuvants, carriers.

Abstract

Process for the preparation of chiral compounds of formula (I) comprising contacting a compound of formula (II) with a source of hydrogen or halide; wherein A is a chiral centre; X is selected from oxygen, sulphur and nitrogen; n is selected from 0 and 1 and is equal to the valence of X less 2; B is a fragment CR 3 2 ; Z is hydrogen or halogen; with the proviso that when X is nitrogen, n is 1, one of R 1 and two of R 2 are hydrogen, BZ is CHPh 2 , the other R 1 and R 2 do not form together a five membered heterocyclic (pyrrolidone) ring; novel intermediates, novel compounds, polymers and libraries thereof and the use thereof as fine chemicals, and compositions thereof.

2.0201 (AM)

DECLARATION AND POWER OF ATTORNEY U.S.A.

ALL PATENTS, INCLUDING DESIGN
FOR APPLICATION BASED ON PCT; PARIS CONVENTION;
NON PRIORITY; OR PROVISIONAL APPLICATIONS

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101 As a below named inventor, I declare that my residence, post office address and citizenship are stated below next to my name, the information given herein is true, that I believe that I am the original, first and sole inventor (if only one name is listed at 201 below), or an original, first and joint inventor (if plural inventors are named below at 201-203, or on additional sheets attached hereto) of the subject matter which is claimed and for which patent is sought on the invention entitled:

102 **PROCESS FOR PREPARING CHIRAL COMPOUNDS**

which is described and claimed in:
- [X] PCT International Application No. **PCT/GB99/04031** filed **6 December 1999**
- [ ] the attached specification
- [ ] the specification in application Serial No. _____ filed _____ (if applicable) and amended on _____

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.
I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.
I hereby claim foreign priority benefits under Title 35, United States Code, §119 (a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

104 Prior Foreign Application(s)

(Number)	(Country)	(Day/Month/Year Filed)	Priority Claimed Yes	No
9826700.8	United Kingdom (GB)	5 December 1998	[X]	[ ]
			[ ]	[ ]
			[ ]	[ ]

103 I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below:

Application No. _____ Filing Date _____ Application No. _____ Filing Date _____

105 I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.)	(Filing Date)	(Status: patented, pending, abandoned)

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorneys (Registration No.) to prosecute this application, receive and act on instructions from my agent, and transact all business in the Patent and Trademark Office connected therewith. HARVEY B. JACOBSON, JR. (20,851), JOHN CLARKE HOLMAN (22,768), MARVIN R. STERN (20,640); ALLEN S. MELSER (27,215); MICHAEL R. SLOBASKY (28,421); JONATHAN L. SCHERER (29,851); IRWIN M. AISENBERG (19,007); WILLIAM E. PLAYER (31,409); YOON S. HAM (45,307) and NATHANIEL A. HUMPHRIES (22,772)

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	POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE OR COUNTRY	ZIP CODE

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SIGNATURE OF INVENTOR 201*	SIGNATURE OF INVENTOR 202*	SIGNATURE OF INVENTOR 203*
DATE 25-5-01	DATE	DATE

[ ] Additional inventors are named on separately numbered sheets attached hereto.